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NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Beta-blockers and traumatic brain injury: a systematic review, meta-analysis, and Eastern Association for the Surgery of Trauma guideline.

Bibliographic Source(s)

Alali AS, Mukherjee K, McCredie VA, Golan E, Shah PS, Bardes JM, Hamblin SE, Haut ER, Jackson JC, Khwaja K, Patel NJ, Raj SR, Wilson LD, Nathens AB, Patel MB. Beta-blockers and traumatic brain injury: a systematic review, meta-analysis, and Eastern Association for the Surgery of Trauma guideline. Ann Surg. 2017 Dec;266(6):952-61. [75 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
YES	Multidisciplinary Group

UNKNOWN	Methodologist Involvement
▮▯▯▯▯	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
▮▮▮▮▮	Search Strategy
▮▮▮▮▮	Study Selection
▮▮▮▮▮	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
▮▮▮▮▮	Grading the Quality or Strength of Evidence
▮▮▮▮▮	Benefits and Harms of Recommendations
▮▮▮▮▮	Evidence Summary Supporting Recommendations
▮▮▮▮▮	Rating the Strength of Recommendations
▮▮▮▮▮	Specific and Unambiguous Articulation of Recommendations
▮▮▯▯▯	External Review
▮▯▯▯▯	Updating

Recommendations

Major Recommendations

The strength of recommendation (strong or weak/conditional) and levels of evidence (high, moderate, low or very low) are defined at the end of the "Major Recommendations" field.

Recommendation

In adults with acute traumatic brain injury (TBI) with no contraindications for β-blockers, the authors conditionally recommend the use of in-hospital β-blockers provided that hypotension (defined as systolic blood pressure <90 mm Hg) and symptomatic bradycardia (defined as heart rate <50 with symptoms) are avoided. The evidence is limited about whether these thresholds are too restrictive or irrelevant, but it would be cavalier to employ permissive hypotensive strategies in the face of known TBI outside of clinical trials. The majority of cohort studies included patients with Head Abbreviated Injury Scale (AIS) of 4 to 5. Therefore, the authors limit the recommendation to patients with severe TBI who are admitted to intensive care unit (ICU) where monitoring for and prevention of adverse cardiovascular events is feasible. Although this recommendation is based on a synthesis of very low-quality studies, most of these studies demonstrate a consistent effect and do not report significant cardiopulmonary harm from administration of β-blockers. However, the authors cannot provide a recommendation on when to initiate β-blockers, which β-blockers to use, or how to titrate β-blockers to a specific heart rate, blood pressure, and/or length of time.

Definitions

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Methodology Levels for Rating the Quality of Evidence

Quality Level	Definitions
High	Very confident that the true effect lies close to estimate of effect
Moderate	Moderate effect; true effect is likely close to estimate of effect but may be substantially different
Low	Limited confidence; true effect may be substantially different from estimate of effect
Very Low	Little confidence; true effect likely substantially different from estimate of effect

GRADE Definition of Strong and Weak Recommendation

	Strong Recommendation	Weak/Conditional Recommendation
For patients	Most patients would want the recommended course of action.	Most patients would want the recommended course of action, but many would not.
For clinicians	Most patients should receive the recommended course of action.	Different choices will exist for different patients, and clinicians should help patients decide.
For policy makers	Recommended course should be adopted as policy.	Considerable debate and stakeholder involvement needed to make policy.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Acute traumatic brain injury (TBI)

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Critical Care

Emergency Medicine

Neurology

Intended Users

Physicians

Guideline Objective(s)

To determine if β-blockers improve outcomes after acute traumatic brain injury (TBI)

Target Population

Adult patients ≥16 years with acute traumatic brain injury (TBI)

Interventions and Practices Considered

In-hospital beta (β)-blockers

Major Outcomes Considered

- Mortality
- Functional recovery or impairment
- Quality of life
- Cardiopulmonary morbidity (e.g., hypotension, bradycardia, bronchospasm, and/or congestive heart failure)

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Methods

Objective

The Population, Intervention, Comparator, and Outcomes (PICO) question was structured as follows:

> Population: in adults with acute traumatic brain injury (TBI),
> Intervention: in-hospital β-blockers should be used,
> Comparator: in-hospital β-blockers should not be used,
> Outcome: to improve mortality, functional outcomes, quality of life outcomes, without worsening cardiopulmonary morbidity (e.g., hypotension, bradycardia, bronchospasm, and/or congestive heart failure).

Study Eligibility

The protocol was registered with the PROSPERO international prospective register of systematic reviews (Registration Number: CRD42016048547). This study is transparently built upon a previously published systematic review, using similar methods and eligibility criteria. The authors searched for randomized controlled trials (RCTs), quasirandomized and nonrandomized controlled trials, and cohort studies (prospective and retrospective) comparing TBI patients who received in-hospital β-blockers after injury to those who did not. They excluded case reports, letters to the editor, articles in the lay press, abstracts,

and review articles. RCTs and observational studies were analyzed separately, as a direct comparison between the estimates of observational studies and RCTs could be misleading.

Population

The authors included studies that involved adult patients aged ≥16 years with acute TBI of any severity requiring hospital admission.

Interventions and Comparators

All forms of in-hospital β-blockers were included, provided they were given during the hospital stay and continued for any duration of time. The comparison group could have received either placebo or no treatment. The authors included any dose of β-blockers and planned sensitivity analyses if different dose and regimens were utilized.

Outcome Measures

Per Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, outcomes were chosen by the team and rated in importance from 1 to 9, with scores of 7 to 9 representing critical outcomes. The critical outcomes were in-hospital mortality, functional recovery, and quality of life with scores of 9, 8, and 7 respectively. The important (i.e., secondary) outcomes are all related to cardiopulmonary morbidity. The authors broadly accepted functional outcome, as assessed using the Glasgow Outcome Score (GOS) scale, Extended Glasgow Outcome Score (GOSE) scale, Functional Independence Measure (FIM), or Disability Rating Scale (DRS). Similarly, they allowed quality of life metrics that used any standardized scale. Secondary outcomes consisted of common cardiopulmonary adverse effects of β-blockers, such as cardiac biomarker elevation, arrhythmia, clinically significant hypotension (i.e., systolic blood pressure <90 mm Hg, which required fluid resuscitation, discontinuation of the study drug, and/or an inotropic agent), clinically significant bradycardia (i.e., bradycardia requiring a temporary pacemaker, a sympathomimetic agent, atropine, or discontinuation of the study drug), bronchospasm, and/or congestive heart failure.

Information Sources

Similar to the original systematic review and meta-analysis on this topic, the authors searched MEDLINE (from January 1, 1950), EMBASE (from January 1, 1980), and Cochrane Central Register of Controlled Trials (CENTRAL, all years). The search was not restricted by date, language, or publication status. The search was last updated on May 9, 2016. The search strategy was based on the MEDLINE search strategy (see the Supplementary Material [see the "Availability of Companion Documents" field]), and was modified as necessary for the other databases. In addition, they searched the reference lists of relevant articles.

Number of Source Documents

Data were extracted from 9 included studies encompassing 2005 unique traumatic brain injury (TBI) patients with β-blocker treatment and 6240 unique controls. Refer to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 1) in the original guideline document.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Methodology Levels for Rating the Quality of Evidence

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Low	Limited confidence; true effect may be substantially different from estimate of effect
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Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Collection and Analysis

Two authors independently examined all of the abstracts of the studies identified by the search and determined the eligibility of each study. Any disagreements were resolved by consensus and including a third author. They scanned the titles and abstracts of every record retrieved to determine which of the studies should be assessed further. If it was clear from the title and abstract that the article was irrelevant, the article was rejected. The full manuscripts of the remaining articles were then retrieved.

Data abstraction forms were created and used to collect the relevant data from the included studies. Two authors independently extracted data on patients, methods, interventions (or exposures in the cohort studies), outcomes and results.

Risk of Bias Assessment

Two authors independently assessed the risk of bias for each included study. Any disagreement was resolved through discussion and consensus. Each included study was classified as a randomized controlled trial (RCT) or a cohort study, and the risk of bias was assessed differently for each type of study. For RCTs, they used the Cochrane Collaboration's tool of assessing risk of bias according to the following domains: sequence generation, allocation concealment, blinding of outcomes, incomplete outcome data, selective outcome reporting, and baseline imbalances. For cohort studies, selection of the exposed and unexposed cohorts, the comparability of the cohorts, the assessment of the outcomes, and the adequacy of follow-up were addressed using the Newcastle-Ottawa Scale (NOS) (see the Supplementary Material, Figure 1 [see the "Availability of Companion Documents" field]). The scale was modified to include important traumatic brain injury (TBI) prognostic variables (age, pupillary reactivity and Glasgow Coma Scale [GCS] Score) under the comparability category, and therefore allowed the reviewers to optimize the applicability of the scale to the TBI cohort studies. Selection for these prognostic variables was based on the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) Core prognostic model. When considering comparability in the modified NOS, the authors assessed whether these important variables were adjusted for in a multivariate analysis (e.g., age, GCS score, pupillary reaction).

Quantitative Assessment

The authors calculated the odds ratio (OR) to measure the treatment effect for the dichotomous outcomes with corresponding 95% confidence intervals (CI). The generic inverse variance method was used when the included study reported only the odds ratio (OR) and its standard error. Clinical heterogeneity across the studies was assessed by examining the details of the subjects, the baseline data, and the interventions and the outcomes to determine whether the studies were sufficiently similar.

Statistical heterogeneity was determined using the I2 statistic and the Chi-square test. They used a funnel plot to assess for reporting bias (see Supplementary Material, Figure 2).

The authors used the Review Manager software (RevMan 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to conduct a quantitative analysis. They performed a meta-analysis using a random-effect model because there was a suggestion statistical heterogeneity between the studies, although there was no evidence of clinical heterogeneity.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Not stated

Rating Scheme for the Strength of the Recommendations

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Definition of Strong and Weak Recommendation

	Strong Recommendation	Weak/Conditional Recommendation
For patients	Most patients would want the recommended course of action.	Most patients would want the recommended course of action, but many would not.
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For policy makers	Recommended course should be adopted as policy.	Considerable debate and stakeholder involvement needed to make policy.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

The authors thank the Eastern Association for the Surgery of Trauma (EAST) membership for feedback during this process, and the EAST Guidelines Committee for the presubmission peer-review.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- In the included studies, exposure to β-blockers after traumatic brain injury (TBI) was associated with a reduction of in-hospital mortality.
- Treatment with β-adrenergic receptor antagonists offers a potentially beneficial approach to blunting the cascade of sympathetic activation after TBI.

Potential Harms

Common cardiopulmonary adverse effects of β-blockers include cardiac biomarker elevation, arrhythmia, clinically significant hypotension (i.e., systolic blood pressure <90 mm Hg, which required fluid resuscitation, discontinuation of the study drug, and/or an inotropic agent), clinically significant bradycardia (i.e., bradycardia requiring a temporary pacemaker, a sympathomimetic agent, atropine, or discontinuation of the study drug), bronchospasm, and/or congestive heart failure.

Qualifying Statements

Qualifying Statements

- The Eastern Association for the Surgery of Trauma (EAST) is a multi-disciplinary professional society committed to improving the care of injured patients. The Guideline Section of EAST develops and disseminates evidence-based information to increase the scientific knowledge needed to enhance patient and clinical decision-making, improve health care quality, and promote efficiency in the organization of public and private systems of health care delivery. Unless specifically stated otherwise, the opinions expressed and statements made in this publication reflect the authors' personal observations and do not imply endorsement by nor official policy of EAST.
- "Clinical practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."* These guidelines are not fixed protocols that must be followed, but are intended for health care professionals and providers to consider. While they identify and describe generally recommended courses of intervention, they are not presented as a substitute for the advice of a physician or other knowledgeable health care professional or provider. Individual patients may require different treatments from those specified in a given guideline. Guidelines are not entirely inclusive or exclusive of all methods of reasonable care that can obtain/produce the same results. While guidelines can be written that take into account variations in clinical settings, resources, or common patient characteristics, they cannot address the unique needs of each patient nor the combination of resources available to a particular community or health care professional or provider. Deviations from clinical practice guidelines may be justified by individual circumstances. Thus, guidelines must be applied based on individual patient needs using professional judgment.

*Institute of Medicine. Clinical practice guidelines: directions for a new program. MJ Field and KN Lohr (eds) Washington, DC: National Academy Press. 1990: pg 39.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Alali AS, Mukherjee K, McCredie VA, Golan E, Shah PS, Bardes JM, Hamblin SE, Haut ER, Jackson JC, Khwaja K, Patel NJ, Raj SR, Wilson LD, Nathens AB, Patel MB. Beta-blockers and traumatic brain injury: a systematic review, meta-analysis, and Eastern Association for the Surgery of Trauma guideline. Ann Surg. 2017 Dec;266(6):952-61. [75 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2017 Dec

Guideline Developer(s)

Eastern Association for the Surgery of Trauma - Professional Association

Source(s) of Funding

Eastern Association for the Surgery of Trauma (EAST)

Guideline Committee

Eastern Association for the Surgery of Trauma (EAST) Guidelines Committee

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Financial Disclosures/Conflicts of Interest

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The authors report no conflicts of interest.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available for purchase from the Annals of Surgery Web site .

Availability of Companion Documents

The following is available:

> Kerwin AJ, Haut ER, Burns JB, Como JJ, Haider A, Stassen N, Dahm P, Eastern Association for the Surgery of Trauma Practice Management Guidelines Ad Hoc Committee. The Eastern Association of the Surgery of Trauma approach to practice management guideline development using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. J Trauma Acute Care Surg. 2012 Nov;73(5 Suppl 4):S283-7. Available from the Eastern Association for the Surgery of Trauma (EAST) Web site .

Supplemental digital content is available from the Journal of Trauma and Acute Care Surgery Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on April 12, 2018. The information was verified by the guideline developer on May 15, 2018.

This NEATS assessment was completed by ECRI Institute on April 12, 2018. The information was verified by the guideline developer on May 15, 2018.

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